DISSERTATION ON

PATTERNS AND PREVALENCE OF
CONGENITAL MALFORMATIONS

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CERTIFICATE

This is to certify that the work embodied in the dissertation entitled "PATTERNS AND PREVALENCE OF CONGENITAL MALFORMATIONS" has been carried out by Dr. S. LAVANYA during the period between March 2005 & March 2008 in the Institute of Obstetrics & Gynaecology, Madras Medical College, Chennai for the partial fulfillment of MD BRANCH II OBSTETRICS AND GYNAECOLOGY Degree Examination.

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A Happy Mother Is Obstetrician's Pride

A Healthy baby is Nation's pride

This clearly picturises the dynamic role of obstetricians in shaping a happy house, prosperous nation and healthy third generation. With the advent of tremendous advancement of paediatric care, investigations and surgical skills, a new horizon has developed in improving the human stock and decrease the perinatal mortality, the lion share of which is congenital malformations[2].

Thanks to the development of modern technology of ultrasound, MRI, amniocentesis, chorionic villous sampling and Percutaneous umbilical blood sampling which have aided in prenatal diagnosis and has avoided unnecessary surgery, false hopes to the mother and embarrassment to the obstetrician who is the first paediatrician.

The rapid development of technology allowing early and accurate prenatal diagnosis of fetal disorder has revolutionised the practice of obstetrics over 20 years. Beginning with simple cytogenetics[17] to detect chromosomal abnormality in amniotic fluid cells, there are new methods that permit rapid detection of mutant genes by using minute quantities of fetal DNA[37]. These techniques coupled with molecular genetics allow

detection of a list of inherited conditions that is expanding[8] almost daily. Of paramount importance is the ability to provide counselling regarding various screening, diagnostic technique and treatment options.

REVIEW OF LITERATURE

Potter defined congenital malformation as an " abnormality of structure detected at birth or during first few weeks of life[26] ". It can be expanded to include functional disturbances in the organs.

Congenital conditions can be referred to as diseases, defects, disorders, anomalies, or simply genetic differences. The usage overlaps, but also involves a valued judgement as to the harmfulness of the condition.

MALFORMATION : The structure is programmed to develop abnormally.

DEFORMATION : Genetically normal tissue destined to develop abnormally due to forces imposed by uterine environment.

DISRUPTION : More severe change in the form or function that occurs in genetically normal tissue when subject to specific insult[19].

EMBROGENESIS

Fertilization occurs in the fallopian tube from few hours to no more than a day after ovulation[35].

Slow cleavage in 3 days

↓

Morula formed in tube enters uterus

↓ 7 days

Embryo hatching and blastocyst implantation

ORGANOGENESIS

3rd week : Neural plate develops from ectoderm

Cardiogenic plate develops from mesoderm

End of 3rd week : Fore and hind gut from endoderm.

Closure of anterior & posterior neural pore is completed on 26th and 27th day respectively[24].

ETIOLOGY

About 3% of newborns have a "major physical anomaly", meaning a physical anomaly that has cosmetic or functional significance.

Congenital malformations involving the brain are the largest group at 10 per 1000 live births, compared to heart at 8 per 1000, kidneys at 4 per 1000, and limbs at 1 per 1000. All other physical anomalies have a combined incidence of 6 per 1000 live births[16].

Congenital malformations of the heart have the highest risk of death in infancy, accounting for 28% of infant deaths due to birth defects, while chromosomal abnormalities and respiratory abnormalities each account for 15%, and brain malformations about 12%[42].

The cause of 40-60% of congenital physical anomalies (birth defects) in humans is unknown. These are referred to as sporadic birth defects, a term that implies an unknown cause, random occurrence, and a low recurrence risk for future children[25]. For 20-25% of anomalies there seems to be a "multifactorial" cause, meaning a complex interaction of multiple minor genetic abnormalities with environmental risk factors. Another 10-13% of anomalies have a purely environmental cause (e.g. infections, illness, or drug abuse in the mother). Only 12-25% of anomalies have a purely genetic cause. Of these, the majority are chromosomal abnormalities[41].

Genetic causes of congenital anomalies include inheritance of abnormal genes from the parents, as well as new mutations in one of the

germ cells that gave rise to the fetus.

3 basic categories

1) Numerical defects- Aneuploidy, Polyploidy

2) Structural defects - Deletions, Inversions, Translocation.

3) Mosaicism[7].

NUMERICAL DEFECTS

Trisomy is the most common and of that Down's is the common cytogenetic abnormality[28].

MATERNAL AGE	INCIDENCE
25-30	1 in 1400
30-35	1 in 900
35-40	1 in 350
40-45	1 in 100
>45	1 in 25

Paternal age has no role in the risk factor for Down's, but there is an increased risk of spontaneous new mutations causing autosomal dominant diseases[29].

85% - Due to meiotic non dysjunction of chromosome, sporadic

in occurrence and associated with rising maternal age.

3-5% - Due to translocation, familial in occurrence, no association with maternal age.

PHENOTYPE: Marked hypotonia, protruded tongue, small head with flat occiput, flat nasal bridge, up-slanting palpebral fissures, single palmar crease. Associated major anomalies include endocardial cushion defects, Gastro intestinal atresia, leukemia and thyroid disease.

RECURRENCE RISK[30]

FATHER KARYOTYPE	MOTHER KARYOTYPE	RISK
Normal	Normal	< 1 %
Translocation 13/21, 14/21, 21/22	Normal	2.3 %
Normal	Translocation	11.9%
Translocation 21/21	Translocation 21/21	100%

Other trisomies like 18 and 13 result in recognisable life threatening pattern of malformations. Monosomy conceptuses die prior to implantation and universally incompatible with life[36].

STRUCTURAL ABNORMALITIES

DELETION: A portion of chromosome is missing and the errors are described by the location of two break points within the chromosome. Most deletions occur during meiosis and result from misalignments during pairing of homologous chromosomes[38].

TRANSLOCATION

1. RECIPROCAL TRANSLOCATION is a rearrangement of chromosomal material in which breaks occur in two different chromosomes and the fragments are exchanged before the breaks are repaired. The rearranged chromosomes are termed derivative chromosomes. If no chromosomal material is gained or lost it is called balanced translocation[6].

2. ROBERTSONIAN TRANSLOCATION results when the long arms of two individual acrocenteric chromosomes fuse at the centromere to form one. Fusion at the centromere results in the loss of one centromere and *satellite regions*[10] which comprise the short arms.

3. INVERSIONS: Result when two breaks occur in the same chromosome and the intervening genetic material is inverted before the breaks are repaired. Inversions cause problems in chromosome

alignment and hence the carrier has high risk to produce abnormal offspring[18].

4. MOSAICISM: It is defined as two or more cytogenetically distinct cell lines in the same individual. The phenotypic expression depends on many factors like whether the abnormal cells involve the placenta, fetus, or some combination[23].

SEX CHROMOSOMAL ABNORMALITIES

TURNER'S syndrome - 45(XO) only monosomy compatible with life. Prevalence in live born neonates is 1 in 5000. It is associated with 20% of 1st trimester abortions. Features include short stature, shield chest, congenital lymphedema, webbed neck, bone abnormalities. Coarctation of aorta, duodenal atresia are major causes of death in this syndrome[27].

KLINEFELTER'S syndrome - 47 XXY associated with tall stature, enunchoid proportions, failure to develop secondary sexual characteristics, cryptorchidism, gynaecomastia and mental retardation[22].

SINGLE GENE (MENDELIAN) DISORDERS

Mendelian disorders are caused by a mutation in the single gene or locus in one or both the members of a gene pair.

Types

- Autosomal dominant.
- Autosomal recessive.
- X-linked diseases.

TERATOGENS

Environmental causes of congenital anomalies are referred to as teratogens. These are generally problems with the mother. Teratogens can include dietary deficiencies, toxins, or infections. For example, dietary deficiency of maternal folic acid is associated with spina bifida. Ingestion of harmful substances by the mother (e.g, alcohol, mercury, or prescription drugs such as phenytoin) can cause recognisable combinations of birth defects[15].

The greatest risk of a malformation due to environmental exposure to a teratogen is between the third and eighth week of gestation. Before this time, any damage to the embryo is likely to result in fatality and the baby will not be born. After eight weeks, the fetus and its organs are more developed and less sensitive to teratogenic incidents.

INFECTIONS

Several infections which a mother can contract during pregnancy

can also be teratogenic. These are referred to as the TORCH infections.

TOXOPLASMOSIS

1. Hydrocephalus
2. Microcephaly
3. Chorioretinitis

RUBELLA[4]

1. Cataract
2. Cardiac defects
3. Deafness
4. Glaucoma
5. Microcornea
6. Mental retardation

CYTOMEGALOVIRUS[5]

1. Microcephaly
2. Mental retardation
3. Chorioretinitis
4. Sensorineural deafness
5. Thrombotic thrombocytopenic purpura

VARICELLA ZOSTER

1. Microcephaly
2. Microphthalmia
3. Hydranencephaly
4. Skin vesicles and scars

SYPHILIS

1. Vesiculo bullous lesions
2. Saber - shin
3. Generalised lymphadenopathy
4. Saddle nose.

DIABETES MELLITUS

Pre-gestational diabetes is more notorious to cause fetal embryopathy. The incidence shoots upto 5-6% (2 fold higher than normal population). High HbA1c levels directly correlate with the incidence of malformations rising to more than 50% if levels are more than 10^9.

CENTRAL NERVOUS SYSTEM	Anencephaly **Holoproscencephaly** Encephalocele
HEART AND GREAT VESSELS	Ventricular septal defect Atrial septal defect

	Transposition of great vessels Coarctation of aorta
SKELETAL&SPINAL	Caudal regression syndrome
GENITOURINARY	Renal agenesis Ureteral duplication
GASTROINTESTINAL	Anal atresia

TERATOGENIC DRUGS

In 1979 Food and drug administration classified drugs into 5 categories[12]

CATEGORY A: No fetal risk e.g. multi vitamins.

CATEGORY B : Animal studies revealed no risk but no human studies available. e.g. Penicillin

CATEGORY C : No adequate studies in animals and humans available. Adverse effects in animals have been reported but no human data.

CATEGORY D : Evidence of fetal risk exist, but benefits outweigh the risk.

CATEGORY X : Proven risk.e.g. Thalidomide

PROVEN TERATOGENS[11]

COMPOUND	MAJOR EFFECT
Thalidomide	Phacomelia
Diethyl stilbosterol	Genital tract abnormalities
Warfarin	**Nasal hypoplasia, bone stippling**
Androgens	**Masculanisation of female fetus**
Folic acid antagonist	Craniofacial defects, growth retardation
Anticonvulsants	Craniofacial defects, Neural tube defect, development delay
Retinoic acid	Craniofacial, cardiac, thymic abnormality
Alcohol	Craniofacial defects, development delay

MULTIFACTORIAL OCCURRENCE

For 20-25% of anomalies there seems to be a "multifactorial" cause, meaning a complex interaction of multiple minor genetic abnormalities with environmental risk factors[21]. Recurrence risk of subsequent affected child is 1-5 %. Common anomalies having multifactorial inheritance are cardiovascular defects, neural tube defect, cleft lip, cleft palate, congenital diaphragmatic hernia, pyloric stenosis, club foot.

IDIOPATHIC ETIOLOGY

Hydrocephalus, renal anomalies, abdominal wall defects, diaphragmatic hernia do not show a definite etiology.

CLASSIFICATION OF MALFORMATIONS

RCOG in 1997 classified malformations into,

- LETHAL malformations
- SEVERE - Possible survival, severe long-term morbidity
- MODERATE - Short and long term morbidity.

LETHAL MALFORMATIONS

CNS	**Anencephaly**
URINARY TRACT	Bilateral renal agenesis
MUSCULO SKELETAL	Lethal osteochondro dysplasia
SKIN	Lethal icthyosis congenita
VARIOUS	Body wall limb complex, giant hygroma

SEVERE MALFORMATIONS

CNS	Microcephaly, hydrocepalus, holoproscencephaly, spina bifida, encephalocele
RESPIRATORY	Pulmonary hypoplasia, sequestration, Pierre robbin sequence, tracheal stenosis

CARDIAC	Defects requiring intervention within 12 months of life except PDA and ASD
GASTRO INTESTINAL	Esophageal atresia, TOF, omphalocele, gastroschisis, intestinal atresia, hirschprung's, ectopic anus, EHBA
URINARY TRACT	Unilateral renel agenesis, renal cystic disease, severe obstructive uropathy, posterior urethral valve.
GENITAL	Absent uterus
MUSCULO SKELETAL	Diaphragmatic hernia,arthogryposis multiplex, severe deformity of spine, absence of limb
SKIN	Ectodermal dysplasia of skin

MODERATE MALFORMATIONS

RESPIRATORY	Septal deviation, choanal atresia, laryngocele
CARDIAC	Defects other than complex anomalies
URINARY	Hydronephrosis, ureteral duplication, vesico ureteral reflux, urachal anomaly
GENITAL	Imperforate hymen, hypospadias, penile abnormalities
MUSCULO SKELETAL	Craniostosis, synostosis, hip dysplasia
EYE, EAR, FACE	Microtia, aniridia, eyelid defects, cataract, facial clefts

CENTRAL NERVOUS SYSTEM ANOMALIES

NEURAL TUBE DEFCTS

Neural tube defects occurs in 1.6 per 1000 live births.[1.]

1. ANENCEPHALY

- The most common nervous system malformation.
- More frequent in females, thought to occur around 28 days of gestation, severe neurologic impairment.
- Anterior end of the neural tube presents as large skull defect and exposed brain, posterior fossa often spared.

2. ENCEPHALOCELE

Protrusion of brain parenchyma through small defect in skull. It is a common association with many chromosomal defects and many syndromes.

3. SPINA BIFIDA

- **Occulta** – Has intact meninges and cord, may have skin dimple, hair tuft and usually asymptomatic.
- **Meningocele** - Cystic outpouching of meninges.
- **Myelomeningocele** - More common than meningocele, most commonly lumbosacral with cord and meninges in cyst, may be

covered by skin & present with lower cord symptoms (legs, bladder, bowel).

4. ARNOLD CHIARI MALFORMATIONS

TYPE 1 Protrusion of cerebellar tonsils down into foramen with hydrocephalus, hydro - syringomyelia

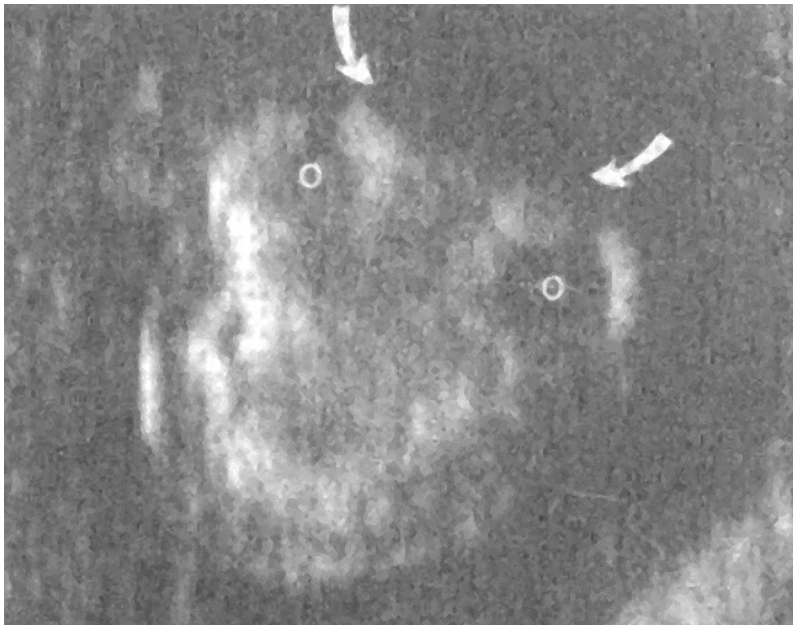
TYPE II Vermis extension through foramen magnum, medullary kinking, midbrain beaking associated hydrocephalus, myelomeningocele, aqueductal stenosis, hydro-syringomyelia

TYPE III Occipital encephalocele

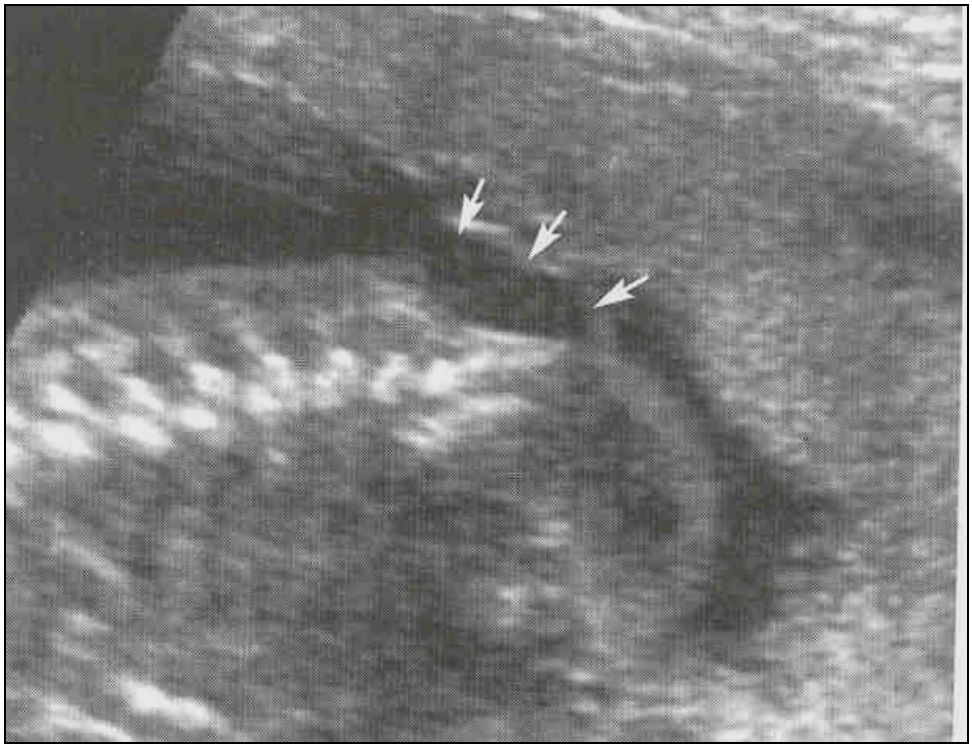
ANENCEPHALY

‘ Frog eye ’

appearance



MENINGOMYELOCELE



PRE NATAL DIAGNOSIS

Prenatal diagnosis identifies the structural and functional abnormalities in an unborn fetus.

GOALS OF PRENATAL DIAGNOSIS

- Detection of major abnormalities
- Informative counselling
- Offers selective termination of pregnancy
- Mental preparation
- Intra-uterine fetal therapy
- Optimise delivery

Prenatal diagnosis is recommended in the following cases

- The pregnant woman is 35 years or older at the time of delivery[39].
- She or her parents have had a previous child with a chromosomal abnormality.
- She has a history of recurrent abortions, or her husband's previous wife experienced several miscarriages.

- A history of parental consanguinity is present.
- The pregnant woman is affected with type 1 diabetes mellitus, epilepsy, or myotonic dystrophy.
- She is exposed to viral infections, such as rubella or cytomegalovirus.
- The mother is exposed to excessive medication or to environmental hazards.
- In her or her spouse's family, a history of Down syndrome or some other chromosomal abnormality is present.
- A history of single gene disorder is present in her or her spouse's family.
- Her male relatives have Duchenne muscular dystrophy or severe hemophilia.
- She is suspected of having some other harmful gene on her X chromosomes.
- The fetus is diagnosed in utero to have some hereditary error of metabolism.
- The fetus is detected to be at increased risk for a Neural tube defect

PRENATAL SCREENING

Prenatal screening is achieved by Biochemical, Sonological and Genetic assessment.

DOWN'S SYNDROME SCREENING

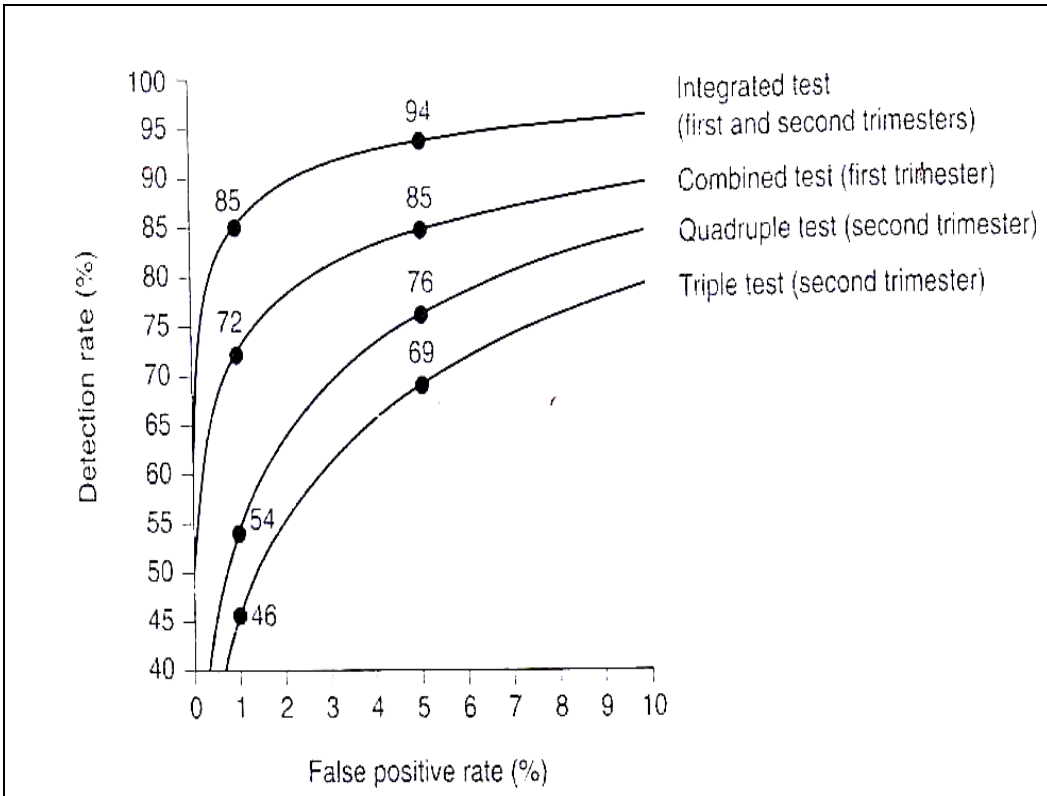
FIRST TRIMESTER

Combined test- Placenta Associated Plasma Protein A + Human Chorionic Gonadotrophin + Nuchal thickness picks up 85% of cases.

SECOND TRIMESTER

Quadruple test-↓ Maternal Serum Alpha Feto Protein + ↑ Beta-Human Chorionic Gonadotrophin +↓ Estradiol + Inhibin has 75% sensitivity.

AFP is a glycoprotein produced by yolk sac, liver, intestinal tract. Concentration is higher in fetus upto 13 weeks, thereafter maternal serum shows a steep rise. The MSAFP test has the greatest sensitivity between 16-18 weeks gestation, but it also can be performed between 15-22 weeks gestation. A combination of the MSAFP test and ultrasonography detects almost all cases of anencephaly and most cases of spina bifida. Also, a NTD can be distinguished from other fetal defects, such as abdominal wall defects, by the use of an acetylcholinesterase test carried out on amniotic fluid obtained by amniocentesis. If the level of acetylcholinesterase rises along with Amniotic fluid AFP, it is suspected as a condition of a Neural tube defect (Nadel, 1990)



INCREASED AFP	DECREASED AFP
Neural tube defect, intestinal obstruction, sacrococcygeal teratoma, abdominal defects, renal anomalies, urinary obstruction, skin defects, multifetal gestation, low birth weight, Intra uterine fetal demise, underestimated gestational age, maternal hepatoma.	Trisomies, gestational trophoblastic disease, Intra uterine fetal demise, high maternal weight, over estimated gestational age.

ULTRASOUND

Ultrasound hints STRUCTURAL ABNORMALITY and picks up 40% of structural malformations, directs towards chromosomal abnormalities, aids other prenatal diagnostic procedures and points other co existent major anomaly. Targeted scan is between 18 to 22 weeks[32].

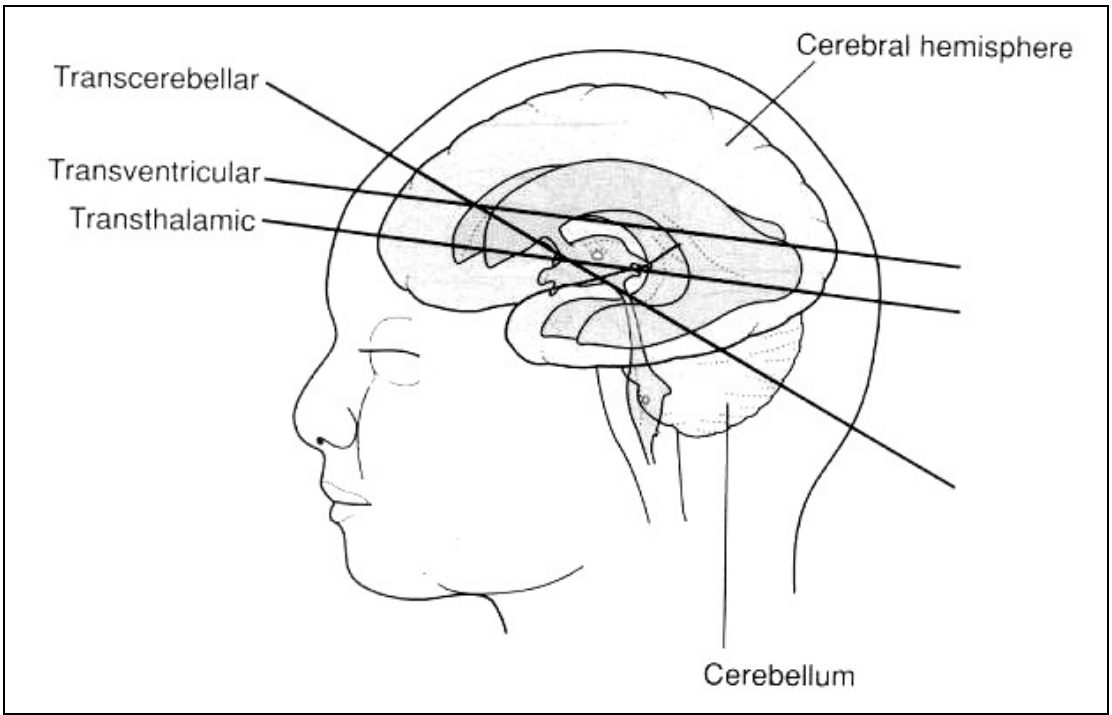
Methodological approach includes viewing head, spine, chest abdomen and limbs. Three views in imaging head:

TRANSTHALAMIC

- Biparietal diameter (BPD)
- Occipitofrontal diameter (OFD)
- Head circumference (HC)

TRANSVENTRICULAR

Atria of lateral ventricle, echogenic choroid plexus



SALIENT FEATURES OF SPECIFIC ANOMALIES

ANENCEPHALY

1. Absence of vault
2. Short neck
3. Frog face
4. Hydramnios

ENCEPHALOCELE

1. Paracranial mass
2. Skull defect

SPINA BIFIDA

1. Discontinued posterior line
2. Exaggerated spinal curvature

3. Defect in subcutaneous tissue

4. Bulging sac

DIAPHRAGMATIC HERNIA

1. Absent stomach bubble

2. Echogenic bowel loops in thorax

3. Dextrocardia

4. Pulmonary hypoplasia.

DUODENAL ATRESIA

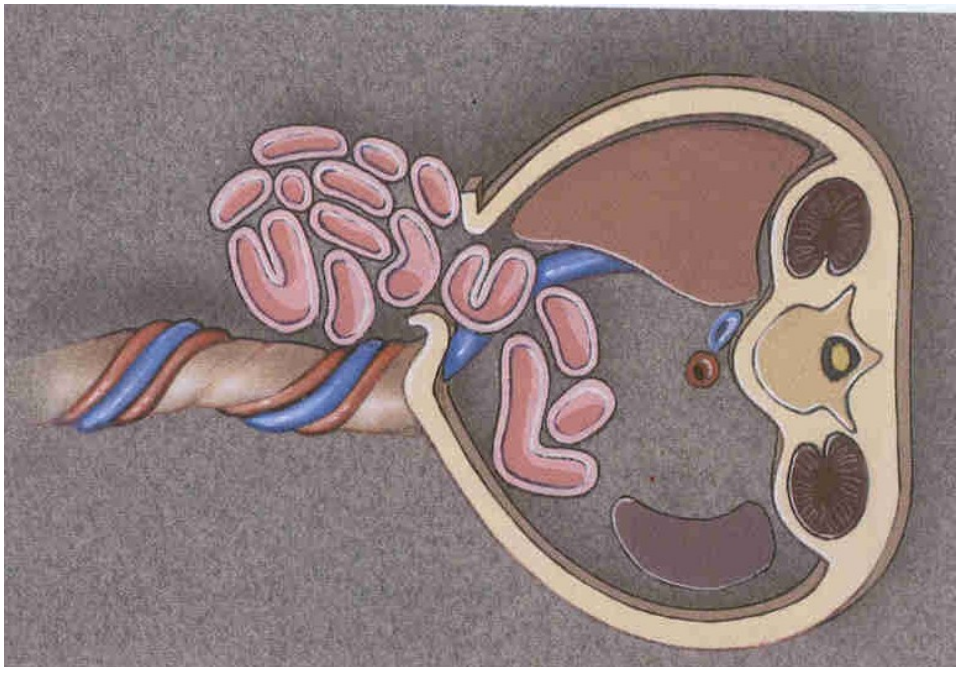
1. Double bubble sign

2. Polyhydramnios

RENAL AGENESIS

1. Absent kidney

2. Hyperechogenic cyst



FETAL ECHOCARDIOGRAPHY

Fetal echocardiography can be performed at 15 weeks gestation and beyond. When this technique is used with duplex or colour flow Doppler, it can identify a number of major structural cardiac defects and rhythm disturbances (Copel, 1987).

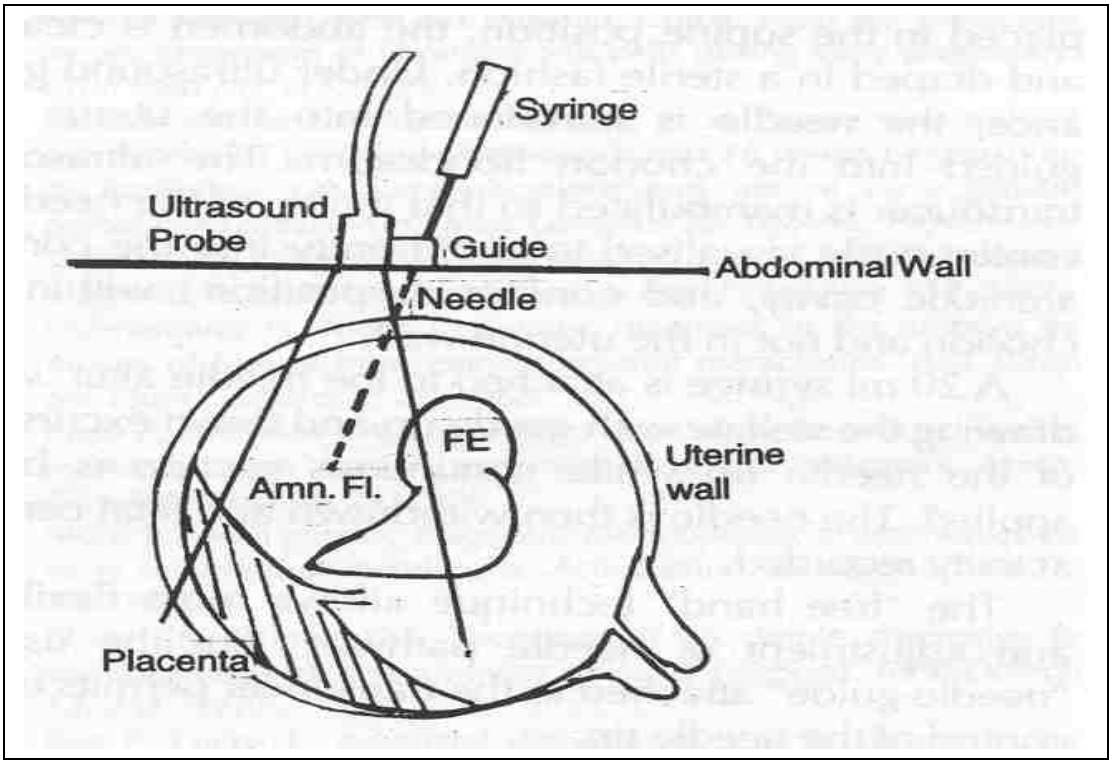
MRI can be a better option when severe oligohydramnios obscures the imaging.

INVASIVE PROCEDURES

Amniocentesis is an invasive, well-established, safe, reliable, and accurate procedure performed between 14-20 weeks of pregnancy. Amniocentesis is advised for pregnant women at 35 years or older for detection of chromosomal abnormalities in the fetus[13]. It is performed

under ultrasound guidance. A 22-gauge needle is passed through the mother's lower abdomen into the amniotic cavity inside the uterus, and 10-20 mL of amniotic fluid that contains cells from amnion, fetal skin, fetal lungs, and urinary tract epithelium are collected. These cells are grown in culture for chromosomal, biochemical, and molecular biologic analyses. Supernatant amniotic fluid is used for the measurement of substances, such as Amniotic fluid alpha feto protein, hormones, and enzymes[14].

The results of cytogenetic and biochemical studies on amniotic cell cultures are more than 90% accurate. In the third trimester of pregnancy, the amniotic fluid can be analysed for determination of fetal lung maturity. Risks with amniocentesis are rare but include 0.5-1.0% fetal loss and maternal Rhesus sensitisation[40].



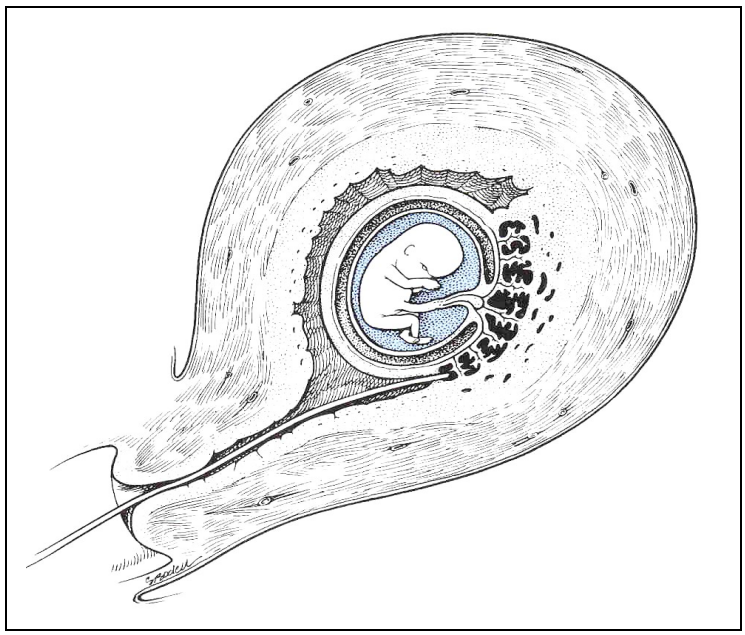
CHORIONIC VILLOUS BIOPSY

Chorionic villous sampling is performed very early in gestation between 9-12 weeks, ideally at 10 weeks gestation. A catheter is passed through the cervix or through the abdominal wall into the uterus under ultrasound guidance, and a sample of chorionic villi surrounding the sac is obtained. The villi are dissected from the decidual tissue, and chromosome analysis is carried out on these cells to determine the karyotype of the fetus[3].

DNA can be extracted from these cells for molecular analysis. DNA analysis of Chorionic villous sampling specimens is helpful for early diagnosis of hemoglobinopathies (Galjaard, 1987). In addition, tissue culture can be initiated on these cells for further studies.

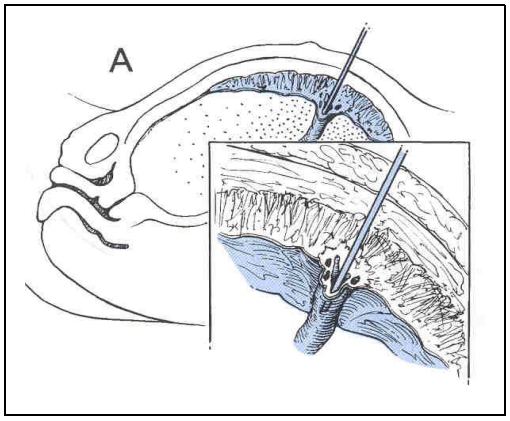
The major advantage of Chorionic villous sampling over amniocentesis is getting quick results and its use in early pregnancy. Abnormalities can be identified at an early stage, and more acceptable decisions about termination of the pregnancy can be taken. Abortion is

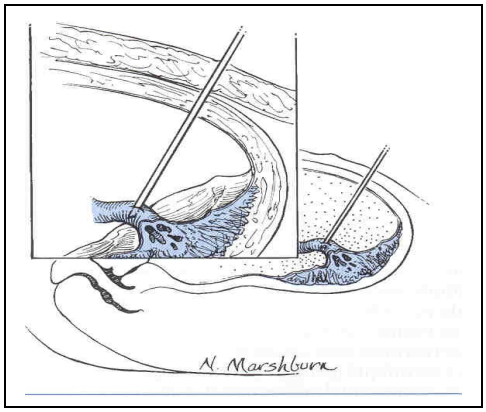
also much safer at this early stage. A disadvantage of Chorionic villous sampling as compared to amniocentesis is 2-3% risk of causing miscarriage, and rarely, Chorionic villous sampling can result with limb defects in the fetus (Burton, 1992). Maternal sensitisation is possible. A higher rate of maternal cell contamination and confined placental mosaicism with Chorionic villous sampling may result in diagnostic ambiguity, leading to the need for additional invasive diagnostic tests (Wang, 1993).



PERCUTANEOUS UMBILICAL BLOOD SAMPLING

Percutaneous umbilical blood sampling or cordocentesis (Daffos, 1985) is a method for fetal blood sampling and is performed after 16 weeks gestation. A needle is inserted into the umbilical cord under ultrasound guidance, and fetal blood is collected from the umbilical vein for chromosome analysis. This technique is also useful for evaluating fetal metabolism and hematologic abnormalities. Complications are bleeding, hematoma, fetal bradycardia and 2.7 % of fetal loss[33].



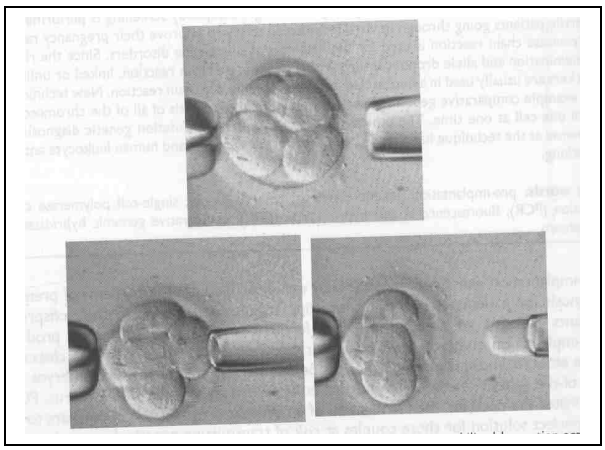


PERCUTANEOUS SKIN BIOPSY

To prenatally diagnose a number of serious skin disorders, such as anhidrotic ectodermal dysplasia, epidermolysis bullosa lethalis, epidermolysis bullosa dystrophica, hypohidrotic ectodermal dysplasia, oculocutaneous albinism, and genetic forms of ichthyosis, percutaneous fetal skin biopsies are taken under ultrasonic guidance between 17-20 weeks gestation[20].

PREIMPLANTATION BIOPSY OF BLASTOCYSTS OBTAINED BY IN VITRO FERTILIZATION

Techniques are being developed to test cells obtained from biopsy of early cleavage stage or blastocyst of pregnancies conceived through in vitro fertilization (Handyside, 1992). These techniques will be helpful for selective transfer and implantation of those pregnancies into the uterus that are not affected by a specific genetic disorder[31]. This approach will be more acceptable to those couples who oppose abortions.



MOLECULAR GENETICS IN DIAGNOSIS[34]

1. Polymerase chain reaction
2. Southern blotting
3. Multiplex polymerase chain reaction
4. Fluorescence in situ hybridisation
5. Linkage analysis

POLYMERASE CHAIN REACTION

Detects numerical abnormalities and point mutations, small insertion or deletions. It includes amplification followed by restriction enzyme analysis and direct sequencing.

SOUTHERN BLOTTING

- Detects large structural rearrangements
- Analysis of DNA from complex genomes
- Detects abnormal DNA sequence
- Example Fragile X syndrome

MULTIPLEX POLYMERASE CHAIN REACTION

This technique is developed for rapid detection of sex and autosomal aneuploides and the greatest advantage is that the results are available within 24 hrs.

FLUOROSCENT IN SITU HYBRIDISATION

FISH is a method of rapid prenatal diagnosis which helps in the detection and localisation of specific DNA sequence

TYPES -Interphase FISH

-Metaphase FISH

INTERPHASE FISH

- It gives faster results within 24 hours
- Requires fewer cells
- 100% success rate
- Fails to detect mosaicism or deletions
- Identifies only 80% of abnormalities
- Only aneuploides of chromosome 21,18,13,X,Y identified

LINKAGE ANALYSIS

Linkage analysis is done for diseases where specific genes are not identified. Polymorphic markers linked to the gene are identified. It can trace mutations from parents.

AIM OF THE STUDY

1. To study the prevalence of congenital malformations in our institute.
2. To study the pattern of malformations.

3. To assess the influence of various risk factors such as Age, Gravidity, Previous Obstetric history, Consanguinity, 1st trimester events on the occurrence of malformations.

MATERIALS & METHODS

The present study was conducted at the INSTITUTE OF OBSTETRICS AND GYNAECOLOGY, a tertiary level Government institution at CHENNAI, Tamil Nadu.

The study was conducted for a period of one year from July 2006 to July 2007 taking into account all the deliveries that occurred in our institution.

The total number of deliveries for the period was 17890.

All the cases booked and unbooked were taken into consideration. Some cases have been diagnosed incidentally in our institution. Some have been referred here with an ultrasound report for either reconfirmation or for termination.

All the cases detected to have congenital malformations by an antenatal ultrasound were analysed by detailed questionnaires. A detailed history regarding the patient and husband's age, parity, occupation, previous obstetric outcomes, family history of malformed babies, degree of consanguinity and the events in the present pregnancy were analysed. Any history of maternal exposure to fever, teratogens, drugs and other

environmental factors were ascertained. Enquiries were put forward with regard to maternal medical diseases like diabetes mellitus. Patients were enquired regarding the intake of preconceptional folate.

Investigations pertaining to the case were done if necessary. Blood sugar was done in indicated cases.

Mediscan systems extended a big hand in helping out in further confirmation of diagnosis and necessary intervention thereafter. Some of the specimens of malformed fetuses were sent to them for autopsy after getting consent from the patient with their fullest co-operation. Genetic counselling was extended to the patients by the genetic department at mediscan systems. Prenatal diagnosis were done to find the karyotype of the fetus when genetic etiology was suspected.

Post delivery, the fetus was examined in detail with regard to obvious external anomalies, weight, sex. A live born baby with anomalies was admitted to the newborn intensive care unit of our hospital and followed up thereafter. Surgically correctable anomalies were referred to the department of paediatric surgery at Institute of child health.

Mother was given genetic counselling before discharge from the

hospital. She was instructed regarding future pregnancy and stressed upon the importance of pre-conceptional folate intake.

Defects which caused serious structural, cosmetic and functional disability requiring surgical or medical management were classified as major anomalies. The rest were categorised as minor anomalies. The major malformations were divided into Central nervous system, Skeletal, Gastro-intestinal, Genitourinary, Cardio vascular system syndromes and miscellaneous disorders. The babies were followed up in the well baby clinics and Institute of Child Health.

TABLE - I

DISTRIBUTION OF CASES WITH AGE

AGE	NO. OF CASES	PERCENTAGE
< 20	54	21%
21-25	123	49%
26-30	62	24%
31-35	10	4%
>36	5	2%
TOTAL	**254**	

The bulk of our deliveries are confined to the age group of 21-25 yrs. Though 50 % of malformations occurred in this age group, there is no actual correlation between age and defects.

TABLE - II

DISTRIBUTION OF CASES WITH PARITY

PARITY	NO. OF CASES	PERCENTAGE
Primi gravida	124	48.8%
Gravida II	79	31.1%
Gravida III	33	12.9%
Gravida IV	14	5.5%
Gravida V	4	1.7%
TOTAL	**254**	

There is no significant relationship between parity and congenital malformations.

TABLE – III

DISTRIBUTION OF CASES WITH CONSANGUINITY

DEGREE	NO.OF CASES	PERCENTAGE
NON CONSANGUINEOUS	191	75.3%
III DEGREE CONSANGUINEOUS	45	17.7%
II DEGREE CONSANGUINEOUS	18	7%
I DEGREE CONSANGUINEOUS	–	
TOTAL	**254**	

In our study the malformations occurred mostly in non-consanguineous marriages. No correlation could be made out between the two.

24 % of the parents were married consanguineously who gave birth to malformed fetuses.

TABLE - IV

DISTRIBUTION OF CASES WITH SEX

SEX	NO. OF CASES	PERCENTAGE
MALE	134	52.7%
FEMALE	111	43.7%
AMBIGUOUS GENITALIA	9	3.5%
TOTAL	**254**	

The malformations showed slight predilection towards male sex.

INCIDENCE OF PREVIOUS PREGNANCY WASTAGE

56 → (22%)

INCIDENCE OF PREVIOUS MALFORMATIONS

28 → (11%)

Around 22 % of malformed babies were born to mothers with previous history of pregnancy wastage and 11 % had previous malformed

babies. This shows there is a genetic role playing important in the etiology of malformations.

TABLE - V

OUTCOME IN MALFORMED FETUSES

OUTCOME	CASES	TOTAL
LIVE BIRTHS	101	17175
MEDICAL TERMINATION OF PREGNANCY	102	1410
INTRA UTERINE DEATH	51	656

The outcome of malformations are dependent on the gestational age at detection. Earlier they are picked up, more the number of recommended termination . 7.3 % of the terminations were done for malformations.

TABLE - VI

CORRELATION BETWEEN MEDICAL ILLNESS & MALFORMATIONS

FEVER	13
GESTATIONAL DIABETES	8
EPILEPSY	2
TORCH	3
DRUGS	2

Maternal febrile illness in the first trimester had a definite predeliction for malformations as pointed out in previous studies.

Infant of diabetic mothers on evaluation showed a higher rate of cardiac and neural defects.

One baby had fetal Hydantoin syndrome, the mother had been taking phenytoin through out her pregnancy.

TORCH screening is not routinely done for all patients, but three of the mothers with recurrent pregnancy wastage showed increased titre.

TABLE - VI

INCIDENCE OF VARIOUS MALFORMATIONS

SYSTEM	INCIDENCE
CENTRAL NERVOUS SYSTEM	131 (51%)
SYNDROMES	44
CARDIOVASCULAR SYSTEM	19
SKELETAL	17
FACE	16
GENITO URINARY TRACT	9
DIAPHRAGMATIC HERNIA	8
GASTRO INTESTINAL TRACT	7
SACROCOCCYGEAL TERATOMA	3

The most common malformations encountered in our hospital were Central nervous system defects. The reason sought is they are picked up more by antenatal Ultrasound and most of them are lethal anomalies.

TABLE - VII

INCIDENCE OF VARIOUS CNS MALFORMATIONS

Anencephaly	49
Spinal defects	36
Hydrocephalus	25
Arnold chiari	9
Microcephaly	6
Corpus callosum	3
Holoproscencephaly	3

Anencephaly was the most reported defect followed closely by spinal defects. Peri conceptional folate were not taken by the patients. Only post conceptional folate were taken by few of them.

TABLE - VIII

INCIDENCE OF VARIOUS CARDIAC DEFECTS

Complex cardiac disease	3
Single ventricle	3
Hypoplastic left ventricle	3
Dextrocardia	3
Transposition of great arteries	2
Septal defects	2
Malformed aorta	1
Truncus arteriosus	1
Ebstein anomaly	1

Only major lethal cardiac defects were detected antenatally and at birth which accounted for 7.5 % of malformations.

TABLE - IX

INCIDENCE OF VARIOUS GASTRO INTESTINAL ANOMALIES

Duodenal atresia	1
Tracheo esophageal fistula	1
Omphalocele	3
Gastroschisis	1
Imperforate anus	1

TABLE – X

INCIDENCE OF VARIOUS GUT ANOMALIES

Posterior urethral valve	3
Renal agenesis	2
Polycystic kidney disease	2
Multicystic dysplastic kidney	2

TABLE – XI

INCIDENCE OF VARIOUS SKELETAL ANOMALIES

Polydactyly, syndactyly	9
Short limbs	3
Congenital talipes equino varus	3
Skeletal dysplasia	1
Achondroplasia	1

TABLE – XII

MALFORMATIONS DETECTED BY ULTRASOUND

Detected	190	74.8 %
Not detected	37	14.5%
Ultrasound not done	27	10.7%

Ultrasound could pick up only 75 % of the anomalies. 15 % of the anomalies were missed by routine Ultrasound which were mostly cardio vascular anomalies.

TABLE – XIII

GESTATIONAL AGE AT WHICH MALFORMATIONS WERE DETECTED

Ist trimester	17
IInd trimester	102
IIIrd trimester	71

Most of the anomalies were detected by anomaly scan done in the second trimester.

DISCUSSION

The global incidence of congenital malformations detected at birth is 2-3%. In India, the nation wide prevalence is high. However there is no systematic surveillance for birth defects in India.

In studies from other parts of India, the incidence varied from 0.3% to 3.6%. The rate in the present study is comparable to the studies from Varanasi, Manipal and Allahabad.

A higher incidence of congenital malformations has been reported from centers like PGIMER Chandigarh and JIPMER Pondicherry, which may be because of higher autopsy rates at these centers.

THE INCIDENCE FROM OTHER COUNTRIES

5.5% Afghanistan

3.4% Michigan

0.9% Northampton-shire

ACCORDING TO BIRTH DEFECTS REGISTRY OF INDIA 2006

1. The overall crude birth prevalence is 92.2 per 10000

2. The crude birth prevalence of birth defects was highest in Mumbai, 145 per 10000, followed by Hyderabad, Chennai, least were from West Godavari.

3. Nervous system defects among which neural tube defects were the most prevalent among most system defects across the regions.

4. The prevalence of major anomalies overall, were 25.9 \ 10000 neural tube defects followed by 7.5 \ 10000 of congenital talipes equino varus, least 1.7 \ 10000 of renal cystic anomalies.

RESULTS OF THE PRESENT STUDY

1. The prevalence of malformations is 147 per 10000.

2. Central nervous system defects were the most recognised malformations at birth and formed the bulk of defects accounting of 76\10000. Nervous system malformations are better detected in the antenatal ultrasound than other systems and most of the anomalies are potentially lethal, hence accounting for the higher numbers. Moreover they are quite obvious to the labour room personnel, requiring no additional confirmation by investigations

and imaging.

3. As against the wide prevalence of cardiovascular defects across the total population, the reported prevalence in the present study is extremely less. This joins hands with rest of the studies done in many centres across the country. The reason being;

a) The pick up rate of cardio vascular defects by ultrasound is very low requiring expertise and high resolution machinery.

b) Most of the anomalies are not detected at birth, as they show up symptoms later in the first week of life and more. Only lethal anomalies like complex cardiac disease manifest in the labouring room.

c) Cardiac defects need to be reconfirmed by imaging like Echo and Doppler which are reported later.

d) Around 94 cases of congenital heart disease were suspected and picked up by postnatal follow up of the baby. (stastistics collected from Institute of child health).

e) From this it is inferred that still cardiac defects form the core of congenital defects, for which we need to expertise upon their

detection rate and its prevention.

4. Targeted or anomaly scan has halved the burden of birth defects and help the mother to prepare herself for the termination and plan the future pregnancies. 75 % of the anomalies were picked up in our study by ultrasound. There were of course 15 % missed cases by routine ultrasound. 10% of the mothers had no scan done through out the pregnancy. Some anomalies were picked up later in the third trimester scans, which were un-noticed in the previous scans.

LIMITATIONS OF THE DATA

1. Data not population based.

2. Passive data collection.

3. Most of the minor unimportant anomalies might not have been noticed.

CONCLUSION

Congenital malformations though cannot be prevented totally, can be minimised and if detected earlier will reduce the mental agony in the

mother and her family. It can be minimised by prenatal counselling, peri conceptional folate and prenatal diagnosis

It has become our professional responsibility to identify those couples who are at risk of having abnormal fetus.

Early ante-natal diagnosis results in earlier termination which will decrease the maternal morbitity and the mental health in the mother.

Conditions amenable to surgical correction in the neonatal period or in utero treatment can be planned if possible.

Broader the diagnosis of birth defects made if Obstetricians, Perinatalogist, Sonologist and Laboratory Personnel work hand in hand.

PROFORMA

1. Name :

2. Age :

3. IP No. :

4. Occupation :

5. Education :

6. Socioeconomic status :

7. Father's age :

8. Address :

9. Obstetric code :

10. Periconceptional folic acid intake :

11. Marital history : Consanguinity / degree

12. Family history : Congenital problems in the siblings, parents .

13. Obstetric history :

a. Gravida

b. Parity

c. Abortions

d. Still births

14. Maternal Problems during pregnancy :

a. Fever

b. Drugs

c. TORCH infections

d. Radiation exposure

e. Diabetes

f. Hypertension

g. Others

15. Ultrasound done : Yes / No

16. Gestational age as per ultrasound :

17. USG findings :

18. Date of delivery :

19. Mode of delivery :

20. Status of fetus : live / still born

21. If abortion : Spontaneous / medical termination

22. Sex :

23. Birth weight :

24. Clinical features :

25. Postnatal followup :

ABBREVIATIONS

ASD	- Atrial septal defect
CM	- Consanguineous marriage
CNS	- Central nervous system
CTEV	- Congenital talipes equino varus
DNA	-Deoxy ribonucleic acid
EHBA	-Extra hepatic biliary atresia
GA	- Gestational age
GDM	- Gestational diabetes mellitus
IUD	- Intra uterine demise
LN	- Labour natural
LSCS	- Lower segment caesarean section
MRI	- Magnetic resonance imaging
MSAFP	- Maternal serum alpha feto protein
MTP	- Medical termination of pregnancy

NCM	- Non consanguineous marriage
NTD	- Neural tube defect
PDA	-Patent ductus arteriosus
PUV	- Posterior urethral valve
RCOG	-Royal College Of Obstetrics And Gynaecology
TGA	- Transposition of great arteries
TOF	- Tetrology of Fallot
TORCH	- Toxoplasmosis, Rubella, Cytomegalovirus, Herpes
USG	- Ultrasonography
VBAC	- Vaginal birth after caesarean
YES/ D	- Detected
YES/ ND	- Not detected

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